Review

Management of Otitis Media with Effusion

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Abstract Otitis media with effusion is one of the most common diseases in children. Its treatment remains controversial. Clinical practice guidelines of OME allow watchful waiting for 3 months before treatment if the child with OME is not at risk for speech/language/or learning problems. Tympanostomy tube insertion is the preferred initial procedure when a child becomes a surgical candidate. Complementary or alternative medicine is not recommended as a treatment for OME. This paper provides a systematic review of management of OME, which we hope will be helpful for clinicians.

Key words Otitis media with effusion; clinical protocols; treatment

Abbreviations

OME otitis media with effusion
AOM acute otitis media
COME chronic otitis media with effusion
SOM secretory otitis media
MEE middle ear effusion
L-NAME N (G)-nitro-L-arginine methyl ester
A85783 a platelet activating factor antagonist
sTNERI tumor necrosis factor soluble receptor type I
HL hearing loss
MVTI miringotomy ventilation tube insertion
ET eustachian tube
HRQoL health-related quality of life
FHS functional heath status
RAOM recurrent acute otitis media
LM laser miringotomy
LTMF Laser-assited tympanic membrane fenestration

Otitis media with effusion (OME) is one of the most common diseases in childhood. In the first year of life, > 50% of children will experience OME, increasing to 60% by 2 years, with another peak at age of 6 years. It is a leading cause of conductive hearing loss in children. However, its treatment remains controversial. This paper presents a systematic review of the treatments that may be beneficial for the clinicals. —(Clinicians)

1 Non-surgical managements

1.1 *The "wait and see" approach*

Spontaneous improvement of secretory otitis media (SOM) is common. Type B tympanometry improves in 78% to 88% of ears[1]. OME after untreated acute otitis media (AOM) resolves in 59% of the cases by 1 month (95% CI: 50-68%). OME of unknown duration resolves spontaneously in 28% of the cases by 3 months (95% CI: 68-80%), and in 42% by 6 months (95% CI: 35-49%)[2]. Renko et al showed similar results in a prospective study[3], in which the mean duration of OME was 10.2 days (rang: 1-58 days). A mere 10 out of 90 cases continued to have OME after 29-43 days. Because the natural history of OME is favorable and most interventions (medicine or surgery) may carry adverse effects or sequelae, a 3-month period of observation is recommended before treatment for a child who is not at risk for speech/language/ or learning problems [4]. This 3-month period of watchful waiting may include interval visits at which OME is monitored using pneumatic otoscopy , tympanometry or both. In contrast, chronic OME had only a 26% resolution rate by 6 months and 33% by 1 year[1]. There is only marginal benefit for longer obser-

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vation. Interventions are therefore recommended for chronic OME.

1.2 *Antibiotics*

Although OME is acknowledged as a sterile disease, studies show that the middle ear effusion from children with OME contains bacteria. Bluestone et al[5] analyzed bacterioligic data from 37 studies of AOM and OME conducted at the Otitis Media Research Center at Children's Hospital of Pittsburgh from 1980–1989. In these studies, 7,396 aspirates were obtained from 5,099 patients. Some 4,589 aspirates were from patients in 10 studies involving children with OME who underwent tympanostomy tube insertion. Haemopbilus influenzae was the most common organism found in OME aspirates at 15% (23% in AOM), followed by Moraxella catarrbalis at 10% (14% in AOM). Streptococcus pneumoniae was found in 7% of aspirates from children with OME and 35% of aspirates from children with AOM. During the 10 years of the study, an increase in β–lactamase producing organisms, both *H.influenzae* and *M.catarrbalis*, was noted. At the same time, cultures of chronic MEE from Japan and Finland also showed *H.influenzae* to be the most common pathogen isolated (20.2% and 8%), followed by *S.pneumoniae* (10.6% and 4.3%), and M. catarrbalis (2.3% and 3.5%)[6]. Rayner et al[7] collected a total 93 effusion specimens from pediatric outpatients seen for myringotomy and tube placement for chronic (> 3 months) OME (median age: 17 months). Eleven (11.8%) of the 93 specimens was tested positive by culture, PCR, and RT–PCR for *H influenzae*. Twenty nine specimens were positive by RT–PCR for H influenzae–specific mRNA. These bacteria may constitute a fundamental factor in the etiology, prognosis and treatment. From their studies on OME, Mandel et al[8] concluded that antibiotics might be useful in selected patients, particularly those with chronic OME (3 months or longer of bilateral effusion or 6 months or longer of unilateral effusion) for whom surgery was being considered. A one–time short course of antibiotic might allow cancellation or at least postponement of a surgical procedure. This is particularly beneficial in spring/summer time when one would like to avoid placing tubes in the ears and placing the child at risk for otorrhea due to water exposure. However, the long–term efficacy is not sure and unnecessary use of antibiotic increases bacteria resistance to these drugs. Antibiotics efficient against sensitive bacteria can result in improvement of OME. Culture and sensitive test before antibiotic use are therefore recommended.

1.3 *Steroids*

Steroids are used commonly in clinical managements of OME, either systemic or topical (instillation of steroids in the middle ear). It is hypothesized that steroids may clear effusion by (1) stabilizing membrane phospholipid breakdown thus preventing formation of arachidonic acid and associated inflammatory mediators; (2) shrinking peritubal lymphoid tissue; (3) enhancing secretion of Eustachian tube surfactant; and (4) reducing middle ear fluid viscosity[9]. Christopher et al[10] designed a systematic review to examine evidence for or against treating OME with systemic or topical nasal steroids. The odds ratio for persisting OME after short–term follow–up was 0.22 (95% confidence interval: 0.08–0.63) in children treated with oral steroids as compared with a control and 0.32 (95% confidence interval: 0.20–0.52) in children treated with oral steroids plus an antibiotic as compared with antibiotic treatment only. They concluded that steroids alone or in combination with an antibiotic led to accelerated OME resolution in short–term. However, there is no evidence to support long–term benefit from treating hearing loss associated with OME with either oral or topical nasal steroids. These treatments are not recommended at the present time. Dhooge et al[11] and Butler et al[12] made the same conclusions. Butler et al emphasized documentation of pre–treatment hearing loss, longer follow–ups and ideally incusion of health–related quality of life and hearing assessments in future studies. Further studies are needed for convincing evidence for steroid treatment for OME.

1.4 *Antihistamines and/or decongestants*

Histamine, found in middle ear effusion, is a potent pharmacological mediator released at an early stage of allergic reaction or general inflammatory process, which increases permeability of small blood vessels. In addition, histamine can cause mucociliary dysfunction in the tubotympanum area, resulting in middle ear effusion since cilia have a significant role in eliminating middle ear effusions[13]. Theoretically, antihistamines may help

reduce histamine-related allergic elements and decongestants may result in mucosal shrinkage and improvement of Eustachian tube patency. Antihistamines and decongestants are popular interventions for OME to "dry up the fluid" and "open the Eustachian". Witmer et al concluded that pharmacologic treatment had significant effect in its resolving OME when compared to no treatment (P=0.0017), although the effect size was weak (R=0.07)[14]. In contrast, a Cochrane review by Griffin GH et al[15] showed that those treated with antihistamines and/or decongestants experienced 11% more side effects than those who recived no treatment. No statistical or clinical benefit was found for any of the interventions studied. Because the pooled data demonstrated no benefit but possible harm from use of antihistamines or decongestants, alone or in combination with other management measures in OME, they recommended against their use. Other studies[16, 17] have also failed to demonstrate any practical impact of these drugs in SOM. Clinical practice guidelines reflect this opinion on the use of antihistamines and/or decongestants[4]. Adverse effects from using these drugs include insomnia, hyperactivity, drowsiness, behavioral change, and bloodpressure variability. At present, although many clinicians still use the antihistamine/decongestants to delay surgery, they should be advised against.

1.5 *Surfactant*

In the year of 1963, Flisberg et al pointed out that there was a substance in the Eustachian tube that could reduce the surface-tension[18]. Studies show more sphingomyelin and less phosphatidylcholine in the Eustachian tube and nose than in the lung, while phosphatidylethanolamine has the same distribution in both places[19]. Surfactant-producing epithelium in the ET is similar to type II pneumocytes[20]. The phosphatidylcholine/sphigomyrlin ratio is significantly lower in Eustachian tube mucus from children with secretory otitis media than otologically healthy children[19], indicating that change of surfactant may be a cause of OME. Normal Eustachian tube fuctioning depends on several mechanical properties, including the ET opening pressure (P_{open}), compliance (ETC) and hysteresis (η). Surfactant plays an important role in regulating the functions of ET. In a gerbil model, exogenous surfactant resulted in a dramatic decrease in Eustachian tube opening pressure in both normal ears and those with effusion[21]. Samir et al[22] came to the same conclusion in their study, where removal of the normal mucosa did not significantly alter Popen but resulted in a decrease in ETC and η ($P<0.05$). Treatment of the mucosa with Infasurf was effective in reducing Popen and restoring both ETC and η to baseline values ($P<0.05$). This may indicate that increasing surfactant in the Eustachian tube is beneficial in reducing persistent OME.

1.6 *Vaccines*

OME may be the continuum of AOM and acquisition of viruses and bacteria in the nasopharynx is considered to be the first essential step in the pathogenesis of OME. Vaccination against these pathogens for children prone to OME or AOM may be effective in preventing additional recurrences. In a randomised controlled double-blin trial to explore the effect of a pneumococcal conjugate vaccine in reducing the risk of OME, Straetemans et al[23] concluded that vaccination appeared to reduce the point prevalence of OME in children without older siblings. This effect was not apparent in children with older siblings. Ozgur SK et al[24] also showed that influenza vaccine was effective in reducing AOM and OME episodes in 6 to 60-month-old day care children, especially during the influenza season. However, in the trail by Van Heerbeek et al[25], the overall recurrence rate of bilateral OME was 50%. Combined pneumococcal conjugate and polysaccharide vaccination did not prevent recurrence of OME among children 2 to 8 years of age previously known to have persistent OME. Therefore, they concluded that pneumococcal vaccines were not indicated for treatment of children suffering from recurrent OME. Similarly, according to Brouwer et al[26], pneumococcal vaccination has no beneficial effect compared with control vaccination against HRQoL or FHS in children 1 to 7 years old with RAOM. Additional studies are apparently needed to address these controversial opinions.

1.7 *Cytokine Inhibitors*

Cytokines play an important role as initiators, mediators and regulators of middle ear inflammation and subsequent molecular-pathological processes in middle ear tissues, leading to histopathological changes in the mid-

dle ear cavity. The existence of high concentration of pro-inflammatory (TNFα, TNFβ, IL1β, IFNγ, IL-6 and IL-8), immunoregulatory (IL-2 and IL-10) and allergic cytokines (IL-4 and IL-5) in the middle ear effusion support the hypothesis that the cytokines can contribute to the conversion of a inflammatory process to a chronic state[27]. The imbalance in the ratio of pro-inflammatory cytokines and inhibitors may lead to the inflammatory process in COME[28]. After inoculation with recombinant Il-1—IL-1beta, middle ear effusion through the eardrum has been found to be similar with injection of endotoxin. Anti-IL-1 receptor antibodies inhibit the pathological changes induced by the endotoxin[29]. In a study by Kim et al[30], the L-NAME, A85783 and sTNFRI groups showed significantly reduced capillary permeability, subepithelial edema and inflammatory cell infiltration in comparison with the group treated with LPS. They concluded that the L-NAME, A85783, and sTNFRI could be alternative treatments for OME. However, similar effect has yet to be shown in human. It is hoped that cytokine inhibitors will have a role in treatment of OME in human in the future.

1.8 *Other medical treatments*

Other medical treatments are also used in management of OME. Mucolytics, for example, have a dispersing action on the excessively viscous mucus in the Eustachian tube. The herbal medicine sirei-to is also used in the treatment of OME to resolve the inflammation and immune response associated with SOM. Their effects need to be evaluated in future studies.

1.9 *Inflation*

Because of the low cost and absence of adverse effects it is reasonable to consider autoinflation whilst awaiting natural resolution of OME. The efficacy of inflation is highly dependent on the timing and frequency of the treatment. In a randomized study by Stangerup et al[31], after 2 weeks of autoinflation, tympanometric parameters improved in 64% of the ears, remained unchanged in 34%, and deteriorated in the remaining 2%, compared with control group in which tympanometric findings improved in 15% of ears, remained the same in 71%, and deteriorated in the remaining 14%. Lesinskas[32] got similar results, e.g., middle ear inflation and middle ear inflation plus antibiotics resulted in better treatment outcomes than observation alone. They concluded that daily middle ear inflation was effective for SOM in adult patients. Alper et al[33], however, documented displacement of fluid by inflation from the tympanum to the mastoid and petrous air cells on MRI imaging. This fluid redistribution could result in a false impression of improvement when evaluated using conventional clinical methodologies such as tympanometry and otoscopy. They suggested that repeated air inflation could prevent development of OME in 50% of ears with functional Eustachian tube obstruction. Future research should address the accuracy of treatment outcome evaluations and long-term impact of inflation on developmental changes in children with OME.

2 Surgical treatment

2.1 *Tympanocentesis and medicine injection into the middle ear*

Tympanocentesis in the early stage of OME can restore hearing and tympanic membrane mobility in the majority of patients. Injection of medicines (e.g., steroids, batroxobin, and ambroxol) following aspiration of fluid within the middle ear can be beneficial. Studies have shown that intratympanically injected batroxobin produced better treatment outcomes than the controls in OME[34-37]. However, these studies have involved small size samples and have not reported long-term effects . We expect that more investigations into these treatments will take place in the future.

2.2 *Tympanostomy*

Tympanostomy is performed in case of highly viscous fluid in the middle ear that is difficult to aspirate to facilitate fluid elimination and improve hearing. At present, tympanostomy is rarely performed alone but is often followed by insertion of tympanostomy tubes. Mandel et al[38] showed that mringotomy alone offered no advantage over no surgery in terms of duration of middle-ear effusion, number of AOM episodes, and number of subsequent surgical procedures.

2.3 *Ventilation Tubes*

Tympanostomy tube insertion is the most frequently performed operation in children with OME all over the world, but whether it is free of complications is still being debated. Vlastarakos et al[39] found that complica-

tions associated with tympanostomy tube insertion were more frequent than anticipated, reaching 80% of operated ears under specific circumstances and in certain subgroups of children. The main complications were purulent otorrhea(10–26%) myringosclerosis (39–65%) segmental atrophy(16–75%) atrophic scars and pars flaccida retraction pockets (21–28%) tympanic membrane perforation(3%, but as high as 24% with T–tubes) cholesteatoma(1%) and granulation tissue(5–40%). Furthermore in a study to determine the cost/effectiveness of ventilation tube in comparison with watchful waiting in children with persistent OME Hartman et al[40] found no differences in language development. Given the associated with ventilation tube treatment, it was not recommended as a standard treatment in young children with persistent OME identified in population–based screening. Rovers et al[41] and Paradise et al[42] agreed with this conclusion. They indicated that grommets might be used in young children who grew up in an environment with a high infection load, in older children with bilateral hearing levels of 25 dB HL or greater for at least 12 weeks, or in children with bilateral effusion for at least 6 additional months and in children with unilateral effusion for at least 9 additional months. To avoid the complications associated with tympanostomy tube insertion and balance cost/effectiveness, the ventilation tube insertion should be performed only in selected patients with appropriate indications.

2.5 *Adenoidectomy*

The adenoid may play an important role in the pathogenesis of OME. Adenoid hypertrophy can cause mechanical obstruction of the Eustachian tube. The adenoid can also be the source of bacteria infection which can induce inflammation of the middle ear. Petri et al[43] have suggested that the adenoid may provide a microenvironment for the generation of $CD4^+$, $CD45RO^+$, L–$selectin^-$, $CXCR4^+$ and $CCR5^+$ T lymphocytes(a lymphocyte phenotype found in the middle ear effusion). When chronic adenoid infection is suspected, adenoidectomy may be beneficial in treating otitis media in children who are older than 4 years of age and who have previously undergone tympanostomy–tube insertion[44]. From a study of 50,000 children over a 24 year period[45], adenoid surgery at the time of MVTI is associated with reduced odds of subsequent MVTI procedure in children with or with out adenoid/tonsil disease with no differences in the length of hospital stay between MVTI alone and MVTI with adenoidectomy. Therefore, the low complication rates with adenoidectomy and short hospital stays made adjunctive adenoidectomy a potentially cost–effective first line management option for OME.

2.6 *Laser myringotomy*

Laser myringotomy is an easy and quick procedure that can be performed in the medical office under topical anesthesia and is suitable for patients with AOM or for those who need short–term ventilation for SOM. The effect of the treatment is dependent on the duration of tympanum perforation. Factors that affect the duration of patency of tympanic membrane include (1) The spot size: Deutsch et al[46] approved that spot sizes of 2.4 and 2.6 mm carried a higher rate of patency than 2.0–mm spot size at 3 weeks following LTMF. (2) The position of perforation: laser mringotomy in the anterior and inferior areas lasted longer than posterior LM[46]. And (3) The ages: from Cohen et al[47], perforation lasted a mean 22 days in adults, 17days in children, and 11 days in infants. In a long–term follow–up study, E Hassmann concluded that the use of CO_2 laser for myringotomy has no negative effect on the function of the cochlea and the healing of the tympanic membrane after myringotomy was uneventful with a low percentage of permanent sequelae[48]. It can be used in the place of ventilation tube in treatment of OME.

2.7 *Retrograde catheterization via the Eustachian tube*

Along with the increasing use of nasal endoscope, retrograde catheterization via the Eustachian tube becoming a new treatment option for OME. A catheter is inserted into the tympanum through the Eustachian tube to clear the middle ear secretion, inject medicines for middle ear mucosa recovery, and balance the pressure in the tympanum. Studies in China[49, 50, 51] have shown that Eustachian tube catheterization is a safe, easy and effective treatment for secretory otitis media. However, some scholars have indicated that Eustachian catheterization is not in physiological for the ET and may cause damage to it. They[52] suggest the long–term effects of the treatment should be investigated before it is used frequently.

2.8 *Mastoid and middle ear surgery*

The indications for mastoid and middle ear surgeries are: 1) recurrent OME after exhausting other management strategies such as tympanocentersis, and ventilation tube insertion; 2) large quantity of fluid in the mastoid air cells on radiography; and 3) progressive development of cholesterol granuloma in the middle ear. Although mastoid and middle ear surgeries have the potential of complete elimination of diseased tissues, restoration of ventilation function of the tympanic sinus and mastoid air cells, as well as prevention of recurrence, they should be performed only when CSOM fails to respond to other treatments [53].

As we know, treatment of OME remains controversial and OME remains the most common disease leading to hearing loss which can impair cognitive language speech and psychosocial development in affected children. Our review of pharmacological treatments, mringotomy and ventilation tube insertion for OME shows no significant difference between drug treatments and mringotomy, but distinct benefits with ventilation tube insertion than the other two. We recommend that surgical insertion of ventilation tube should be considered in a child with OME who is at risk for speech/language/hearing loss/ or learning problems to prevent these problems from occurring. Drug treatments or mringotomy is not recommended because of their unsubstantiated benefits. Other surgical treatments need to be further studies for their long-term effects. It is hoped that continued research efforts will improve treatment outcomes for patients with OME.

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Errata for Volume 3 Number 1

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Table 5 Glucose(GLU) and triglyceride changes (TG)(mean ± SD)

Group	Number		GLU (mm01/L)	TG (mm01/L)
High Dose	10	before	28.89±0.86	0.34±0.06
		after	21.86±1.45$^{**\#\#}$	0.09±0.04$^{**\#\#}$
Low Dose	12	before	28.60±0.95	0.29±0.02
		after	23.28±1.25$^{*\#\#}$	0.15±0.07$^{**\#\#}$
Yu Quan Wan	11	before	28.85±1.02	0.35±0.01
		after	22.62±1.18$^{*\#}$	0.34±0.08$^{**\#}$
Control	10	before	28.76±1.05	0.32±0.07
		after	28.60±1.69	0.32±0.04

$^{*}P < 0.05$, $^{**}P < 0.01$, compared to pretreatment levels. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, compared to the control.

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